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Invasive Infections Caused by *Trichosporon* Species and *Geotrichum capitatum* in Patients with Hematological Malignancies: a Retrospective Multicenter Study from Italy and Review of the Literature

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Trichosporonosis is an uncommon but frequently fatal mycosis in immunocompromised patients. A multicenter retrospective study was conducted to characterize cases of proven or probable invasive trichosporonosis diagnosed over the past 20 years in Italian patients with hematological diseases. Of the 52 cases identified, 17 were classified as *Trichosporon* sp. infections and 35 were attributed to *Geotrichum capitatum*. Acute myeloid leukemia accounted for 65.4% of the cases. The incidence rates of *Trichosporon* sp. and *G. capitatum* infections in acute leukemia patients were 0.4 and 0.5%, respectively. Overall, 76.9% of cases had positive blood cultures. Pulmonary involvement was documented in 26.9% of cases. Death was reported for 57.1% of *G. capitatum* infections and for 64.7% of *Trichosporon* sp. infections. A literature review on trichosporonosis in patients with any underlying disease or condition reveals *G. capitatum* as a predominantly European pathogen, particularly in certain Mediterranean areas, while *Trichosporon* sp. infections are seen with similar frequencies on all continents. The majority of published *Trichosporon* sp. and *G. capitatum* infections occurred in patients with hematological diseases (62.8 and 91.7%, respectively). Well over half of these were suffering from acute leukemia (68 and 84% of patients with *Trichosporon* sp. and *G. capitatum* infections, respectively). Crude mortality rates were 77% for *Trichosporon* spp. and 55.7% for *G. capitatum*. The optimal therapy for trichosporonosis has yet to be identified; however, in vitro experiences are providing encouraging evidence of the potential role of the new triazoles, in particular, voriconazole.

The incidence of invasive fungal infections in patients with hematological malignancies has risen over the last two decades, mainly as a result of the increased use of intensive cytotoxic therapy, allogeneic blood stem cell transplantation, and immunosuppressive therapy. Various groups have stressed the importance of new opportunistic fungal pathogens as causes of life-threatening infections (6, 102). Trichosporonosis is an uncommon but frequently fatal invasive fungal infection in immunocompromised patients, particularly those with hematological malignancies. The pathogens most commonly implicated in invasive trichosporonosis are the yeasts widely referred to as *Trichosporon* sp. and *Geotrichum capitatum*. Over the past decade, the taxonomy of the genus *Trichosporon* has been subjected to extensive revision on the basis of molecular data, and the previously named *T. beigelii* (or *T. cutaneum*) corresponds, in the most recent classification, to six different species: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, and *T. ovoides* (46, 48). Rare cases of systemic infection have also been attributed to other *Trichosporon* species, such as *T. pullulans* and *T. loubieri*. *Geotrichum capitatum*, originally known as *Trichosporon capitatum*, has also undergone extensive reclassification (23, 47, 110). Consensus has yet to be reached on the proper nomenclature for this organism, and it is also referred to by some authors as *Blastoschizomyces capitatus* (105).

Despite the increasing attention being focused on all fungal infections, little is known about the current epidemiology of these emerging opportunistic pathogens. Therefore, we conducted a multicenter retrospective study to characterize cases of invasive trichosporonosis diagnosed over the past 20 years in Italian patients with hematological diseases and reviewed similar cases published to date in the international literature.

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MATERIALS AND METHODS

A total of 15 hospital hematology departments located in 11 regions of Italy participated in the study. All were members of the Infection-Control Program of the Italian Group for Study of Hematologic Disease in Adults (Gruppo Italiano

Malattie Ematologiche dell'Adulto [GIMEMA]). Five of the participating centers were located in northern Italy (in Milan, Turin, Bergamo, Udine, and Bologna), six were in central Italy (in Florence, Pescara, and Ancona and in three centers in Rome), and four were in southern Italy (in Naples, Reggio Calabria, Bari, and San Giovanni Rotondo). In each center, all invasive infections caused by *Trichosporon* sp. or *G. capitatum* observed in patients with hematologic malignancies between January 1983 and December 2002 were retrospectively ascertained and reported to the study coordinator by means of a simple case report. Fungi were identified in all centers according to morphological and biochemical criteria. Morphological studies were carried out with corn meal agar by the observation of mycelium, arthroconidia, and blastoconidia. Morphological confirmation of *G. capitatum* isolates by the observation of the presence of anelloconidia, specific to this fungal species, was performed in only a minority of cases. Biochemical tests were performed by using either a API or VITEK system (BioMerieux Italia, Rome, Italy) or both. The *Trichosporon* sp. isolates from two centers (Rome and Pescara) were available for reidentification according to the new taxonomic classification by using a VITEK 2 system (BioMerieux Italia); the identification of *T. asahii* strains was confirmed by the PCR amplification of rRNA gene fragments by using species-specific primers as described by Sugita et al. (114, 115). For each case, data were collected on patient demographics, underlying condition, presentation and clinical characteristics of the infection, management, and outcome.

Our analysis focused on those infections that could be classified as "proven" or "probable" according to the definitions of opportunistic invasive fungal infections published by the European Organization for Research and Treatment of Cancer Invasive Fungal Infection Cooperative Group (EORTC/IFICG) and National Institute of Allergy and Infectious Disease Mycoses Study Group (NIAID/MSG) (8).

Invasive trichosporonosis was defined as "proven" when one or more of the following criteria were met: (i) blood cultures yielding *Trichosporon* species or *G. capitatum* in patients with temporally related clinical signs and symptoms of infection, (ii) positive CSF culture results, or (iii) biopsy specimens that were culture positive for *Trichosporon* species or *G. capitatum* and presented histopathologic evidence of fungal growth characterized by minimal septate hyphal branching, blastospores, and fragmentation of the mycelium in arthroconidia.

Cases were defined as "probable" when all of the following criteria were met: (i) the presence of at least one host factor criterion (i.e., neutropenia, recent immunosuppressive therapy, or persisting fever refractory to appropriate broad-spectrum antibacterial treatment), (ii) one microbiological criterion, or (iii) one major clinical criterion (i.e., imaging) consistent with infection.

The EORTC/IFICG and NIAID/MSG definitions do not provide specific indications on the significance of *Trichosporon* sp. and *G. capitatum* recovery from respiratory-tract specimens. Our experience indicates, however, that for cases of this type, the microbiological criteria provided for infections caused by molds or *Cryptococcus neoformans* can be applied with a good degree of reliability. Therefore, in keeping with these criteria, patients with pulmonary infiltrates and recovery of *Trichosporon* species or *G. capitatum* from sputum or bronchoalveolar lavage fluid samples in the absence of other pathogens causing opportunistic infections were considered to meet the criteria for "probable" pulmonary infection. Regardless of the isolation of the fungus from blood, invasive tissue infections were defined as focal when the involvement of a single organ was documented and as disseminated when two or more organs were involved.

A MEDLINE-based literature search was conducted for the period 1965 to May 2004 to identify all reported cases of invasive trichosporonosis in patients with any underlying condition. The search terms used were "*Trichosporon*" or "*Geotrichum*" or "*Blastoschizomyces*" and "infection"; cases of superficial infection were excluded. For each case found, the following data were recorded, when available: geographical location, patient age and sex, underlying disease or condition, therapy for the underlying disease, site of infection, treatment of the infection, and outcome.

Since the classification and nomenclature of the yeasts in question have undergone numerous modifications over the years, cases identified in our retrospective study and review of the literature were broadly classified as *Trichosporon* sp. infections when the causative agent was identified as any of the following: *T. beigelii*, *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, and *T. ovoides*. Likewise, all infections attributed to *Blastoschizomyces pseudotrichosporon*, *Blastoschizomyces capitatus*, *Trichosporon capitatum*, or *Geotrichum capitatum* were grouped under the heading "*G. capitatum* infections."

To shorten the references section, most of the papers cited in previous reviews (49, 74, 76, 77, 83, 92, 108, 118) have not been included in the References list.

RESULTS

Retrospective study of cases in Italy. Patient population. During the 20-year period examined in our study (January 1983 through December 2002), 52 cases of probable or proven invasive *Trichosporon* sp. or *G. capitatum* infections in patients with hematological malignancies were identified. The characteristics of these cases are summarized in Table 1. The mean age of infected patients was 40.3 years (range, 11 to 65 years), and 35 (67%) patients were male. A total of 17 of the cases were classified as *Trichosporon* sp. infections. They were *T. asahii* in 6 cases and *T. pullulans* in one case. In the remaining 10 cases previously identified as *T. beigelii* a reidentification according to the new taxonomic classification was not possible. A total of 35 cases were attributed to *G. capitatum*. Of the cases included in this series, 24 have been previously published (21, 22, 31, 32, 33, 39, 69, 76).

The most common underlying hematologic malignancy was acute myeloid leukemia, which accounted for 65.4% of the cases. Prior to the onset of infection, 88.5% of the patients had received cytotoxic chemotherapy, and 86.5% had severe neutropenia (polymorphonuclear leukocytes $< 100/mm^3$) at the time of infection.

Epidemiology. Of the 15 participating hematological centers, 8 reported at least one case of *Trichosporon* sp. or *G. capitatum* infection during the 20-year study period. Of the 52 (44.2%) cases, 23 occurred during the first decade of the study period (1983 to 1992) in five different centers; the remaining 29 (55.8%) cases were observed between 1993 and 2002 in seven centers. The regional distribution of the infections is detailed in Fig. 1. All but 1 (97%) of the 35 *G. capitatum* infections occurred in central (29 cases) or southern (5 cases) Italy, and 20 (57%) cases were observed in a single institution in Rome. In particular, in this center 16 cases were observed in the period 1983 to 1985 (76) and only 4 cases were observed in the following 17 years.

During the period 1992 to 2000, a total of 3,420 new cases of acute leukemia in patients over 12 years of age were observed in 13 of the participating centers. (These figures were not available for the other two centers, and none of the 15 centers could supply data for the years before and after the period 1992 to 2000). Of these 3,420 patients, 16 (0.5%) developed *G. capitatum* infections, and *Trichosporon* sp. infections were diagnosed in 15 (0.4%).

Infection. Overall, 44 (84.6%) of the 52 infections were classified as "proven" on the basis of positive blood cultures (40 cases; 76.9%) or histopathology plus positive tissue culture (4 cases), while eight patients (15.4%) had probable infections (Table 1). In 24 (60%) of 40 cases of fungemia, focal or disseminated invasive tissue infection was documented; less commonly (16 cases; 40%), fever was the only sign of infection associated with fungemia. Pulmonary involvement was documented in a total of 14 (26.9%) of 52 cases (eight *G. capitatum* and six *Trichosporon* sp. infections). Eight of these were proven cases (as determined on the basis of blood culture findings in six cases and histopathologic findings in the other two). The other six patients met the criteria for probable pulmonary infection, i.e., fever that was unresponsive to broad-spectrum antibacterial therapy, multiple pulmonary infiltrates, and sputum or bronchoalveolar lavage fluid cultures that grew *G. capi-*

TABLE 1. Characteristics of the 52 cases of *Trichosporon* spp. and *G. capitatum* infections in patients with hematological malignancies from the retrospective study of the GIMEMA Infection Program

Characteristic	No. (%) of *Trichosporon* spp. infections (17 cases)[a]	No. (%) of *G. capitatum* infections (35 cases)
Underlying hematologic malignancy		
Acute myeloid leukemia	8 (47.1)	26 (74.3)
Acute lymphoid leukemia	2 (11.8)	6 (17.1)
Lymphoma	3 (17.6)	
Multiple myeloma	2 (11.8)	2 (5.7)
Chronic myeloid leukemia	1 (5.9)	1 (2.9)
Myelofibrosis in blast crisis	1 (5.9)	
Previous therapy for the underlying hematologic disease		
Chemotherapy	15 (88.2)	30 (85.7)
Allogeneic blood stem cell transplant		4 (11.4)
Autologous blood stem cell transplant	1 (5.9)	1 (2.9)
Steroids	1 (5.9)	
Neutrophil count at diagnosis of infection		
PMN ≤1,000–>500	3 (17.6)	1 (2.9)
PMN ≤ 500/mmc–>100	2 (11.8)	1 (2.9)
PMN ≤ 100/mmc	12 (70.6)	33 (94.3)
Clinical presentation		
Proven infections	15 (88.2)	29 (82.9)
Fungemia (total no. of cases)	14 (82.3)	26 (74.3)
Fungemia without invasive tissue infection	7 (41.2)	9 (25.7)
Fungemia with invasive tissue infection	7 (41.2)[b]	17 (48.6)[d]
Invasive tissue infection without fungemia	1 (5.9)[c]	3 (8.6)[e]
Probable infections	2 (11.8)	6 (17.1)
Focal pulmonary lesions and positive sputum-BAL culture	1 (5.9)	5 (14.3)
Focal renal lesions and positive urine culture	1 (5.9)	1 (2.9)
Antifungal treatment		
Amphotericin B	9 (52.9)	14 (40)
Liposomal amphotericin B	2 (11.8)	4 (11.4)
Amphotericin B plus flucytosine		7 (20)
Fluconazole	3 (17.6)	5 (14.3)
Amphotericin B followed by fluconazole	2 (11.8)	1 (2.9)
Econazole	1 (5.9)	
No therapy		4 (11.4)
Mortality	11 (64.7)	20 (57.1)

[a] In this group are infections identified as *T. asahii* (6 cases) and *T. pullulans* (1 case) according to current taxonomic classification and *Trichosporon* species identified as *T. beigelii* according to previous taxonomic classification (10 cases).
[b] Focal: pulmonary, 4 cases; cutaneous, 1 case; disseminated: 2 cases.
[c] Focal: pulmonary.
[d] Focal: pulmonary, 2 cases; CNS, 1 case; bone, 1 case; disseminated: 13 cases.
[e] Focal: pulmonary, one case; meningitis, one case; disseminated: one case.

tatum (5 cases) or *Trichosporon* spp. (1 case). Of the 52 patients, 2 (3.8%) had proven central nervous system infections caused by *G. capitatum* (focal meningitis in one case and multiple cerebral localizations with fungemia in the other). Two (3.8%) others had probable urinary tract infections documented by multiple urine cultures positive for *G. capitatum* or *Trichosporon* spp. (one case each) and sonographic evidence of renal lesions, and the remaining patient developed *G. capitatum* fungemia followed by documented infection of a intervertebral disk (22). Overall, 2 (11.8%) of 17 *Trichosporon* sp. and 14 (40%) of 35 *G. capitatum* infections were disseminated ($P = 0.04$; odds ratio, 0.20; 95% confidence interval, 0.03 to 1.16).

Therapy and outcome. Various treatment regimens were used, but well over half (33 of 52; 63.5%) of all patients received conventional amphotericin B (alone, associated with flucytosine, or followed by fluconazole) (Table 1). The crude mortality rate was 59.6% (31 of 52 cases): 57.1% of the patients with *G. capitatum* infections and 64.7% infected by *Trichosporon* spp.

Literature review. Infected patients. The literature search yielded 201 reports of trichosporonosis in patients with various types of predisposing conditions, including 24 of the 52 Italian cases described above, which had been reported in previous publications of ours (21, 22, 31, 32, 33, 39, 69, 76). For the present analysis, we also added the 28 unpublished cases of our series, bringing the total number to 396 cases. These included 287 cases classified under the broad heading of *Trichosporon* sp. infections (1, 2, 9, 10, 12, 14–19, 24, 26, 27, 31, 33, 34, 36, 42–45, 49, 50, 53–55, 57, 58–63, 66–69, 71–75, 79–85, 87–94, 98, 103, 104, 111, 112, 116–120, 123, 127–132, 134), 99 infections assigned to the category of *G. capitatum* infections (3, 4, 13, 20–22, 25, 32, 35, 37–39, 50, 52, 70, 76, 77, 93, 95, 97, 100, 101, 106,108, 133), 8 infections caused by *T. pullulans* (56, 64, 65, 86, 109), and 2 attributed to *T. loubieri* (78, 96). The patient characteristics and geographic origins of the cases are summarized in Table 2. The male/female ratio was 2:1 for both *Trichosporon* sp. and *G. capitatum* infections. Hematological diseases, peritoneal dialysis, and solid tumors were the three most commonly reported underlying diseases or conditions in patients with *Trichosporon* sp. infection (62.8, 8.3, and 6.8% of the cases, respectively). The 287 infections we assigned to the category of *Trichosporon* spp. included 28 cases (all reported after 1995) in which the yeast was identified, in accordance with the revised classification, as *T. asahii* (17 infections, including 10 in patients with hematological diseases) (1, 16, 26, 36, 58, 81, 84, 98, 131, 132, plus 6 cases from the present series); *T. inkin* (5 infections, 2 in patients with hematological malignancies) (19, 72, 74, 84, 104); *T. mucoides* (4 infections, none involving patients with hematological malignancies) (45, 92); and *T. cutaneum* or *T. asteroides* (each responsible for 1 infection, both involving patients with hematological malignancies) (18, 66). The vast majority of *G. capitatum* and *T. pullulans* infections occurred in patients with hematological disease (91.7 and 75%, respectively).

The geographic distribution of the reported cases of trichosporonosis varied according to the pathogen involved. *Trichosporon* sp. and *T. pullulans* infections were reported in similar numbers on all the continents, whereas 86 (86.9%) of the 99 cases of *G. capitatum* infection were observed in Europe, in particular, in Italy (38 cases), Spain (30 cases), and France (7 cases). These three Mediterranean countries were thus the source of almost 90% of the European reports of *G. capitatum* disease and roughly three-fourths of all reports in the world literature.

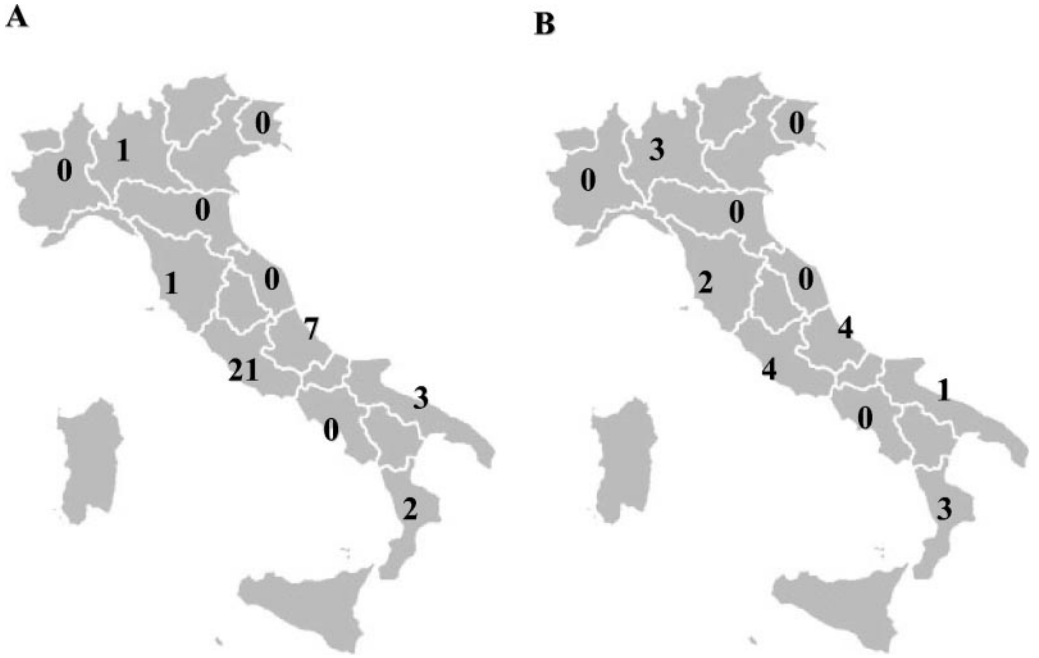

FIG. 1. Regional distribution of 35 cases of *G. capitatum* (A) and 17 cases of *Trichosporon* sp. (B) infection occurring in Italy between 1983 and 2002.

Table 3 shows the clinical characteristics of the 262 cases of invasive trichosporonosis documented for patients with underlying hematological disease. Well over half of these were suffering from acute leukemia (68, 84, and 50% of patients with *Trichosporon* sp., *G. capitatum*, and *T. pullulans* infections, respectively). Overall, 87% of the infected patients had been treated with conventional cytotoxic chemotherapy, and 11% had received allogeneic or autologous blood stem cell transplants. Analysis of cases in which site involvement was specified revealed that the fungal pathogen was isolated from the blood in the majority of patients (74.7% of those infected with *Trichosporon* sp. infections, 77.3% with *G. capitatum* infections, and 50% of those with *T. pullulans* infections). In only a few cases (3.2% for *Trichosporon* spp. and 1.1% for *G. capitatum*) the infection was related to a central venous catheter. Around 50% of all *Trichosporon* sp. and *G. capitatum* infections were classified as disseminated (defined as involvement of two or more organs, with or without fungemia). Disease was restricted to the lungs in fewer than 20% of all cases (16% of patients with *Trichosporon* sp. infection, 19% of those infected with *G. capitatum*). Focal hepatosplenic involvement was reported in 3.2 and 3.4% of *Trichosporon* sp. and *G. capitatum* infections, respectively. Crude mortality rates were higher for *Trichosporon* spp. (77%) than for *G. capitatum* (55.7%) ($P < 0.001$; odds ratio, 2.07; 95% confidence interval, 1.45 to 4.91).

Information on antifungal treatment and outcome were reported for 128 of the *Trichosporon* sp. infections and 83 of those caused by *G. capitatum* (Table 4). All 22 patients who received no antifungal treatment died. Conventional amphotericin B, alone or associated with flucytosine, fluconazole, or itraconazole, was the drug most frequently employed in the initial antifungal regimen, as it was used in 90 (79.6%) of 113 *Trichosporon* sp. infections and 47 (61.8%) of 76 *G. capitatum* infections. Voriconazole was employed as initial antifungal regimen in only two cases of patients with *G. capitatum* infection who died. For both types of infection, survival rates in patients treated with combined therapy were similar to those for patients who received a single drug.

DISCUSSION

The first cases of *G. capitatum* and *T. beigelii* infections were reported in 1965 and 1970, respectively (38, 130). Later, in 1988, *Trichosporon pullulans* (recently renamed *Guehomyces pullulans*) (34) infection was described (56), and in 2003 reports of invasive infections caused by *T. loubieri* began to appear in the literature (78, 96). In 1992 the classification of members of the genus *Trichosporon* was substantially revised by Guého et al. (46), and few years later a new classification was proposed by Sugita et al. (113–115) on the basis of analysis of 26S rRNA sequences. It is now widely accepted that this genus includes 17 species (113), including the 6 that were previously classified as a single species referred to as *T. beigelii* (or, formerly, *T. cutaneum*). These six species, *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, and *T. ovoides*, are all recognized as potential human pathogens, and it has been suggested that each is associated with different types of infection. *T. cutaneum* and *T. asteroides*, for example, seem to be linked with superficial infections, while *T. ovoides* and *T. inkin* are involved in white piedra of the scalp and pubic area, respectively. *T. asahii* and *T. mucoides* have also been isolated from a few patients with white piedra, but they are usually associated with deep-seated infections (48, 113). It is difficult, however, to confirm these correlations, since, in many of the reports in the literature, isolates are identified using the older terms, *T. beigelii* or *T. cutaneum.* To determine which of the

TABLE 2. Characteristics of the 396 cases of invasive *Trichosporon* spp. and *G. capitatum* infections in immunocompromised patients reported in the literature[a]

Characteristic	*Trichosporon* spp. infection[b] (n = 287)	*G. capitatum* infection (n = 99)	*T. pullulans* infection (n = 8)	*T. loubieri* infection (n = 2)
Sex (male/female) [no. of evaluable cases]	138/65 [203]	56/28 [84]	6/1 [7]	1/1 [2]
Mean age (range) [no. of evaluable cases]	40 (1–78) [205]	44 (1–76) [80]	57 (47–65) [7]	50 (45–56) [2]
Underlying disease or condition, no. of evaluable cases	266	96	8	2
Hematological disease, no. of cases (%)	167 (62.8)	88 (91.7)	6 (75)	1 (50)
Solid tumor, no. of cases (%)	18 (6.8)	3 (3.1)	1 (12.5)	
Organ transplant, no. of cases (%)	10 (3.8)	0	1 (12.5)	
Prosthetic cardiac valve, no. of cases (%)	10 (3.8)	2 (2.1)		
Peritoneal dialysis, no. of cases (%)	22 (8.3)	0		
HIV infection, no. of cases (%)	4 (1.5)	0		
Newborn, no. of cases (%)	15 (5.6)	1 (1.0)		
Burn, no. of cases (%)	5 (1.9)	0		
Other diseases or conditions, no. of cases (%)	15 (5.6)	2 (2.1)		1 (50)
Geographic distribution, no. of evaluable cases	283	99	8	2
Europe, no. of cases (%)	78 (27.6)	86 (86.9)	4 (50)	0
Italy	25 (8.8)	38 (38.4)	1 (12.5)	
Spain	9 (3.2)	30 (30.3)		
France	16 (5.6)	7 (7.1)		
Slovakia	9 (3.2)	1 (1.0)	3 (37.5)	
Germany	3 (1.1)	4 (4.0)		
Great Britain	7 (2.5)	3 (3.0)		
Ireland	1 (0.3)	0		
Belgium	5 (1.8)	0		
Sweden	1 (0.3)	0		
Greece	1 (0.3)	0		
The Netherlands	0	1 (1.0)		
Czech Republic	0	1 (1.0)		
Switzerland	0	1 (1.0)		
North America, no. of cases (%)	96 (33.9)	5 (5.0)	3 (37.5)	1 (50)
United States	92 (32.5)	5 (5.0)	3 (37.5)	1 (50)
Canada	4 (1.4)	0	0	
South America, no. of cases (%)	6 (2.1)	0	0	
Brazil	5 (1.8)			
Argentina	1 (0.3)			
Asia, no. of cases (%)	93 (32.9)	7 (7.0)	1 (12.5)	1 (50)
Japan	66 (23.3)	2 (2.0)	1 (12.5)	
Taiwan	10 (3.5)	1 (1.0)		
Turkey	5 (1.8)	0		
Saudi Arabia	3 (1.1)	3 (3.0)		
Korea	2 (0.7)	0		
India	3 (1.1)	1 (1.0)		1 (50)
Lebanon	1 (0.3)	0		
Pakistan	1 (0.3)	0		
China	2 (0.7)	0		
Africa, no. of cases (%)	8 (2.8)	1 (1.0)		
Israel	5 (1.8)	1 (1.0)		
Sudan	2 (0.7)	0		
South Africa	1 (0.3)	0		
Australia, no. of cases (%)	6 (2.1)	0		

[a] Includes the 52 Italian cases described in the present paper.
[b] In this group are infections by *T. asahii* (17 cases), *T. inkin* (5 cases), *T. mucoides* (4 cases), *T. cutaneum* (one case), and *T. asteroides* (one case) according to current taxonomic classification and *Trichosporon* spp. identified as *T. beigelii* according to previous taxonomic classification (259 cases).

newly defined species are the causes of these infections, these isolates would all have to be reidentified, and in many cases, this is probably not feasible. Our search for reports of *Trichosporon* sp. infections yielded 28 cases (including 6 from the present series) in which the yeast was identified according to the new taxonomic classification. All six species were reported as causative agents of invasive disease, and all but *T. mucoides* were implicated in invasive infections in patients with hematological malignancies. Importantly, out of the 16 isolates of our series previously designated as *T. beigelii*, the six available

TABLE 3. Clinical characteristics of the cases of invasive *Trichosporon* sp. and *G. capitatum* infections in patients with hematological diseases reported in literature[a]

Characteristic	No. of cases/total no. of evaluable cases (%)			
	Trichosporon spp[b] (n = 167)	*G. capitatum* (n = 88)	*T. pullulans* (n = 6)	*T. loubieri* (n = 1)
Underlying hematologic disease				
Acute leukemia (unspecified)	21/160 (13.1)	1/88 (1.1)		
Acute myeloid leukemia	67/160 (41.9)	56/88 (63.6)	1/6 (16.7)	
Acute lymphoid leukemia	21/160 (13.1)	16/88 (18.2)	2/6 (33.3)	1 (100)
Lymphoma	17/160 (10.6)	3/88 (3.4)	1/6 (16.7)	
Multiple myeloma	5/160 (3.1)	4/88 (4.5)		
Chronic myeloid leukemia	10/160 (6.2)	3/88 (3.4)		
Chronic lymphoid leukemia	3/160 (1.9)	1/88 (1.1)		
Aplastic anemia	4/160 (2.5)	1/88 (1.1)		
Histiocytosis	3/160 (1.9)	0		
Myelodysplastic syndrome	4/160 (2.5)	3/88 (3.4)		
Other hematological diseases	5/160 (3.1)	0	2/6 (33.3)	
Therapy of the underlying hematologic disease				
Chemotherapy	121/142 (85.2)	72/84 (85.7)	4/6 (66.6)	1 (100)
Allogeneic blood stem cell transplant	14/142 (9.9)	8/84 (4.8)		
Autologous blood stem cell transplant	4/142 (2.8)	2/84 (2.4)		
Other therapies	3/142 (2.1)	2/84 (2.4)	2/6 (33.3)	
Site of infection				
Fungemia, total no. of cases	115/154 (74.7)	68/88 (77.3)	3/6 (50.0)	1 (100)
Fungemia without invasive tissue infection	25/154 (16.2)	14/88 (15.9)	2/6 (33.3)	
Disseminated infection[c]	78/154 (50.6)	41/88 (46.6)	0	1 (100)
Lung[d]	25/154 (16.2)	17/88 (19.3)	2/6 (33.3)	
Meninges[d]	3/154 (1.9)	3/88 (3.4)	0	
Central venous catheter[d]	5/154 (3.2)	1/88 (1.1)	1/6 (16.6)	
Skin[d]	14/154 (9.1)	1/88 (1.1)	1/6 (16.6)	
Liver-spleen[d]	5/154 (3.2)	3/88 (3.4)	0	
Bone and joint[d]	1/154 (0.6)	4/88 (4.5)	0	
Palate[d]	1/154 (0.6)	0	0	
Gut[d]	1/154 (0.6)	1/88 (1.1)	0	
Kidney[d]	1/154 (0.6)	1/88 (1.1)	0	
Esophagus[d]	0	2/88 (2.3)	0	
Mortality	114/148 (77.0)	49/88 (55.7)	2/5 (40.0)	0

[a] Includes the 52 Italian cases from the present study.
[b] In this group are infections by *T. asahii* (10 cases), *T. inkin* (2 cases), *T. cutaneum* (one case), and *T. asteroides* (one case) according to current taxonomic classification and *Trichosporon* species identified as *T. beigelii* according to previous taxonomic classification (153 cases).
[c] With or without fungemia.
[d] Focal invasive tissue infection, with or without fungemia.

for reidentification were all *T. asahii* according to their morphological characteristics and biochemical and molecular profiles.

There is currently no standard classification for *Geotrichum capitatum* (23, 47, 105, 110). It was originally known as *Trichosporon capitatum* and classified among the basidiomycetes. Later, however, in light of its cell wall structure and septal pores and its tendency to produce numerous arthroconidia and few blastoconidia, it was considered to be an ascomycete. The appropriateness of this classification was further supported by the discovery of its sexual form (teleomorph), *Dipodascus capitatus* (23, 37, 110), and it was thus assigned to the genus *Geotrichum*. The subsequent discovery of its ability to produce anelloconidia, as well as arthroconidia and blastoconidia, led Salkin to reclassify *G. capitatum* as the single species of a new genus: *Blastoschizomyces capitatus* (105). However, from a taxonomic point of view, some authors maintain that *G. capitatum* is the correct anamorphic name (48, 108).

G. capitatum and *Trichosporon* spp. are generally indistinguishable from one another on the basis of colony morphology alone. Both form arthroconidia as well as blastoconidia. *G. capitatum* can also produce anelloconidia, which unfortunately may be misidentified as arthroconidia or blastoconidia. Therefore, these two species are usually differentiated by their carbohydrate assimilation patterns and other biochemical properties. *Geotrichum candidum* is a further species with similar colony findings which is differentiated from the other two species by morphology (it produces only arthroconidia) and by biochemical properties.

Our literature review demonstrates that while opportunistic infections with *Trichosporon* species or *G. capitatum* can occur in various types of immunocompromised patients, those with hematological malignancies are by far the most common victims of these infections. Patients of this type accounted for 92, 63, and 75% of invasive *G. capitatum*, *Trichosporon* sp., and *T. pullulans* infections, respectively, and one of the two reported patients with *T. loubieri* infection also had hematologic disease. Of the hematological malignancies mentioned in the reports

TABLE 4. Treatment regimens and outcome for 128 *Trichosporon* spp. and 83 *G. capitatum* infections in patients with hematological diseases

Treatment regimen	No. of cases of survival/total no. of cases (%)	
	Trichosporon spp. infections	*G. capitatum* infections
No therapy	0/15 (0)	0/7 (0)
First-line therapy		
Single-drug regimen	25/78 (32)	29/62 (46.8)
Amphotericin B (AmB)	13/55 (23.6)	13/35 (37.1)
Lipid formulation of AmB	1/3 (33.3)	6/10 (60)
Fluconazole	3/6 (50)	9/10 (90)
Miconazole	5/9 (55.5)	
Voriconazole		0/2 (0)
Other drugs	3/5 (60)	1/5 (20)
Combination regimen	12/35 (34.3)	6/14 (42.9)
AmB + flucytosine	8/26 (30.8)	3/8 (37.5)
AmB + fluconazole or itraconazole	4/9 (44.4)	2/4 (50)
Lipid formulation of AmB + flucytosine		1/2 (50)

we reviewed, acute leukemia, acute myeloid leukemia in particular, was the underlying disease most frequently associated with all these infections. Most of the infected patients had been treated with conventional cytotoxic chemotherapy, and very few had received blood stem cell transplants. The infections usually occurred during a period of profound neutropenia (neutrophil count, less than 100/mm^3).

Although acute leukemia is the major underlying condition in trichosporonosis, its incidence seems to be low even in this group. On the basis of our retrospective study of Italian cases, the incidence rates for *Trichosporon* sp. and *G. capitatum* infections among patients with acute leukemia were only 0.4 and 0.5%, respectively (four cases of *Trichosporon* spp. and five cases of *G. capitatum* per 1,000 adult patients with acute leukemia). It is important to recall, however, that retrospective ascertainment of documented cases of trichosporonosis (and all other fungal diseases) reveals little more than the tip of the mycological iceberg. Unfortunately, there is little information in the literature on the incidence of these infections. In a study of 353 hematology patients undergoing chemotherapy or allogeneic bone marrow transplantation, *G. capitatum* and *Trichosporon* sp. systemic infections were demonstrated with one (0.3%) and two (0.6%) patients, respectively (50). Their low epidemiological impact seems to be confirmed by a surveillance study of fungemia in cancer patients conducted by the IFICG/EORTC (125). In this study, which involved 30 centers and lasted 2 years (1992 to 1994), 269 cases of fungemia were reported but only 5 were caused by *G. capitatum* (2 cases) or *Trichosporon* spp. (3 cases) (unpublished data). On the other hand, the risk of underestimation has been highlighted by findings from an autopsy survey conducted at a university hospital in Japan (118). During the 10-year study period (1983 to 1992), disseminated *Trichosporon* sp. infection was found in 7 (7.7%) of 203 autopsy patients with malignant disease, and only two of these infections had been etiologically diagnosed before death occurred. The others had been misdiagnosed as candidiasis on the basis of clinical findings.

Our experience and review of the literature suggest that the geographic distribution of trichosporonosis is by no means homogeneous. For example, although the 15 hematological centers participating in our study were uniformly distributed throughout the Italian peninsula, all but one of the 35 *G. capitatum* infections reported had occurred in central and southern regions. Furthermore, 20 of the 35 infections occurred in a single center in Rome, whereas in seven of the participating centers, there was not one single case of trichosporonosis during the entire 20-year period examined. It should be underlined that in the Roman institution, the distribution of *G. capitatum* infections was not homogeneous over the years. In fact, 16 of the 20 cases were observed in the period 1983 to 1985 (76) and only 4 cases were observed during the ensuing 17 years. An active search for *G. capitatum* was performed during the first period, but an environmental source of the infection was not found (76). On the other hand, although it does not take the Roman cluster of *G. capitatum* infections into account, the hypothesis of a peculiar geographic distribution of this mycosis continues to be valid. Underdiagnosis might be suspected in some centers, yet all of the hospitals involved in this study had reference microbiology laboratories fully capable of characterizing fungal isolates. Moreover, the case ascertainment rate in *Trichosporon* sp. and *G. capitatum* infections is probably higher than it is with other fungal infections. In fact, the high rate of isolation of these yeasts from the bloodstream (>74%) during a deep infection is in sharp contrast to those reported for most of other opportunistic fungi: for *Candida* spp., <50% (7); for *Aspergillus* spp., 10% (40); for *Fusarium* spp., 56% (11).

Regional variations at the global level also emerged from an earlier review of the literature published through 1988 (76). At this point, *Geotrichum capitatum* and *Trichosporon* sp. infections were both observed almost exclusively in the United States and Europe. However, while *G. capitatum* infections were reported more frequently in Europe (85% of all cases) than in the United States (10%), the frequencies of *Trichosporon* spp. were reversed (15% of cases were reported in Europe and 78% of cases were reported in the United States). Our review, which also included papers published in the last 16 years, indicates that there is still a significantly higher frequency of *G. capitatum* infections in Europe, which now accounts for 87% of the reported cases. Furthermore, 87% of the European cases occurred in Italy, Spain, and France. This finding, together with the marked clustering of our cases in central and southern Italy, seems to suggest that climatic factors might play a selective role in the epidemiology of *G. capitatum* infections. As for *Trichosporon* spp., the previously noted concentration of these infections in the United States was not confirmed by our review. Only around one-third of all reported cases currently come from North America, and similar percentages are now registered for Europe and Asia.

Similar pictures emerge from data collected during the ARTEMIS DISK Surveillance Study, a very recent prospective study conducted in more than 30 countries to identify global trends in the susceptibility of yeast pathogens to fluconazole and voriconazole (51). Isolates collected between June 1997 and December 2002 (unpublished data; reported with permission) in-

cluded 81 *Trichosporon* sp. strains and 40 *G. capitatum* strains. While the former were recovered with roughly identical frequencies in Europe, the Americas, and Asia, 32 (80%) of the 40 *G. capitatum* isolates came from Europe, and over half (18 of 32; 56.3%) of the European isolates were recovered in Italy.

The clinical features of trichosporonosis frequently resemble those of invasive candidosis, although there are some significant differences. *Trichosporon* spp. and *G. capitatum* are isolated from blood in over 70% of invasive infections, and approximately two-thirds of the reported cases of fungemia are associated with clinically or microbiologically documented invasive tissue localization; in a very small number of cases a central venous catheter is the portal of entry of the infection. These clinical features are in contrast with those observed in cancer patients with candidemia, as shown in a large prospective European study on candidemia in cancer patients in which only 10% of patients had a clinically or microbiologically-histologically documented organ involvement and a correlation of fungemia with a central venous catheter was demonstrated in 31% of cases (125). The EORTC/IFICG and NIAID/MSG definitions provide no specific indications on the significance of *Trichosporon* sp. and *G. capitatum* recovery from respiratory-tract specimens (8). Since both microorganisms are potential components of the normal microbial flora of the human digestive and respiratory tracts, it may be difficult to distinguish between colonization and infection. Several groups, however, have demonstrated that the isolation of these yeasts from superficial sites is significantly correlated with the development of invasive infection (50, 54, 76, 128). In a 10-year study at the M. D. Anderson Hospital and Tumor Institute in Houston, Texas, for example, *Trichosporon* spp. were isolated from 79 patients (54). For 60 of these patients, the isolation was believed to reflect colonization, but deep infections were ultimately documented in the remaining 19. Of particular interest is the fact that invasive pulmonary infections were subsequently documented for six of the nine patients whose sputum or bronchial lavage specimens had repeatedly grown *Trichosporon* spp. In another surveillance study (128), isolates of *Trichosporon* spp. or *G. capitatum* were recovered from 15 patients (any site): five were diagnosed as infected, five as possibly infected, and five as colonized. In the latter group, colonization was intermittent and transient. Our group at the Dipartimento di Biotecnologie Cellulari ed Ematologia of the University "La Sapienza" in Rome conducted epidemiologic surveys of *G. capitatum* colonization and infection during the periods 1983 to 1985 (76) and 2001 to 2003 (unpublished data). During the 6 years covered by these two surveys, the yeast was isolated from superficial sites (sputum, oral swab, stool, urine) for 26 patients. For eight (31%) of these patients, stool, urine, or oral colonization was transient, and their clinical courses were all uneventful. However, 13 (50%) cases ultimately satisfied the published criteria for proven invasive infections, and five other patients had radiologically documented diffuse alveolar infiltrates, with sputum yielding *G. capitatum* in the absence of microbiological data supporting other infectious etiologies. Collectively, these experiences support the view that the clinical significance of isolation of these pathogens from sputum in neutropenic patients seems to be comparable with that of molds and *Cryptococcus neoformans*, and for this reason, we and other investigators (77) feel that in the absence of other identifiable pathogens, the recovery of *Trichosporon* spp. or *G. capitatum* from respiratory-tract specimens of patients with clinically documented pneumonia is indicative of probable pulmonary trichosporonosis.

Analysis of the cases reported in our study and those described in the literature reveals no significant differences in the clinicopathological features of deep-seated *G. capitatum*, *Trichosporon* sp., and *T. pullulans* infections in patients with hematological malignancies. However, the rate of mortality attributable to *Trichosporon* spp. and *G. capitatum* in this population appears to be higher than that associated with invasive *Candida* infections (107, 125). In particular, the prognosis was significantly worse for patients with *Trichosporon* sp. infections.

The optimal therapy for trichosporonosis has yet to be identified. In our series and in the cases found in the literature, conventional amphotericin B, alone or associated with other antifungal agents, was the drug most frequently employed in first-line therapy of both *Trichosporon* sp. and *G. capitatum* infections. The low number of cases treated with alternative antifungal regimens does not allow any comparative evaluation of the efficacy of these strategies. Several investigators have proposed dual-drug therapy with amphotericin B and flucytosine as a valid option for both types of trichosporonosis (76, 94, 127), but we found no evidence in the literature that this (or any other) drug combination was more effective than single-drug regimens. As for the newer antifungal drugs, it is currently impossible to make any predictions of their clinical efficacy. The literature contains reports of only a few cases in which voriconazole or caspofungin was used as initial or salvage antifungal therapy (43, 77, 101).

However, in vitro susceptibility findings can be a useful guide in selecting an antifungal regimen for trichosporonosis. In vitro resistance to amphotericin B has been detected in a number of *Trichosporon* sp. strains isolated from neutropenic patients with disseminated trichosporonosis that was refractory to this drug (127). Several groups have demonstrated the in vitro activity of azole antifungals against members of the *Trichosporon* genus, and these drugs have produced favorable responses in animal models (4, 5, 126, 127). However, relatively high fluconazole MICs have been found for some *Trichosporon* isolates (121, 122), and multidrug resistance to amphotericin B, flucytosine, fluconazole, and itraconazole has also been reported (131). In recent studies the new triazoles, voriconazole, posaconazole, and ravuconazole, have displayed potent in vitro activity against isolates of *T. asahii* and other *Trichosporon* species (99), and Falk et al. have reported low voriconazole MICs and minimal fungicidal concentrations for multidrug-resistant isolates of *T. asahii* (30). The high MICs reported thus far for the novel echinocandins, caspofungin, anidulafungin, and FK463, indicate that these agents are unlikely to be effective against *Trichosporon* species (28, 121, 122), and a breakthrough *Trichosporon* sp. infection in a bone marrow transplant recipient during caspofungin prophylaxis has in fact been reported (43).

Data on the antifungal susceptibility of *G. capitatum* are limited (21, 29, 39, 124). We recently investigated the in vitro activities of amphotericin B, flucytosine, fluconazole, itraconazole, and voriconazole against 23 isolates of *G. capitatum* (most of which were the causes of the Italian infections de-

scribed above) (41). The results confirmed previous observations on the high activity of amphotericin B against this species (124) and the reduced susceptibility of certain strains to flucytosine, fluconazole, and itraconazole (21) and revealed voriconazole as a very active drug against this yeast. This profile is consistent with that reported for seven *G. capitatum* isolates recovered from hematology patients with deep infections in a tertiary hospital in Madrid (37).

In conclusion, *Trichosporon* spp. and *G. capitatum* cause life-threatening invasive infections, particularly in neutropenic patients with acute leukemia. The overall incidence of these infections seems to be low, even in leukemic patients, but their distribution is by no means homogeneous, and higher frequencies are observed in certain countries and in certain hematological centers. Our literature review confirms the emergence of *G. capitatum* as a predominantly European pathogen, particularly in certain Mediterranean areas, while *Trichosporon* sp. infections are now being seen with similar frequencies on all continents. Both yeasts cause infections that are clinically similar to invasive candidosis, but they are associated with higher bloodstream recovery rates, more frequent deep organ involvement, and a poorer prognosis. The current body of published clinical data is too limited to allow reliable conclusions on the most effective form of treatment, but in vitro experiences are providing encouraging evidence of the potential role of the new triazoles, in particular voriconazole, in the therapeutic armamentarium against invasive *Trichosporon* sp. and *G. capitatum* infections.

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